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(54) Ranolazine and related piperazines used in the treatment of tissues experiencing a physical or chemical insult

Ranolazin und verwandte Piperazine zur Behandlung von Geweben, von physischen oder chemischen Schäden betroffen

Ranolazine et pipérazines relatés utilisés pour le traitement des tissus éprouvant des blessures physiques ou chimiques

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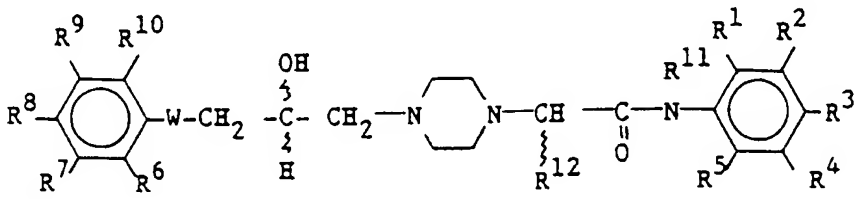
Description

The present invention relates to methods of treatment using ranolazine or another piperazine derivative compound of Formula I, particularly to methods of using ranolazine for treatment of tissues experiencing a physical or chemical insult, and specifically for use in transplants.

Ranolazine, i.e., ±N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-1-piperazine acetamide or 1-[3-(2-methoxyphenoxy)-2-hydroxypropyl]-4-[(2,6-dimethylphenyl)aminocarbonylmethyl]piperazine, and the dihydrochloride salt thereof, and the compounds of Formula I, are described in U.S. Patent No. 4,567,264. Ranolazine is disclosed as a calcium entry blocking compound useful in the treatment of cardiovascular diseases, such as, myocardial infarction. congestive heart failure, angina and arrhythmia.

The anti-ischemic effects of ranolazine have been described in a number of publications, such as, Jain et al., "A PRELIMINARY STUDY OF A NEW ANTI-ANGINAL AGENT", Cardiovascular Drugs and Therapy, Vol. 1, No. 3, p. 252 (October 1987); Allely and Alps, "THE EFFECTS OF THE NOVEL ANTI-ANGINAL AGENT RANOLAZINE (I.D.) IN A CANINE MODEL OF TRANSIENT MYOCARDIAL ISCHAEMIA", Br. J. Pharmacol., 1988, 93, 246P; and by Ferrandon et al., PROTECTIVE EFFECTS OF THE NOVEL ANTI-ISCHAEMIC AGENT RANOLAZINE (RS-43285) IN PERFUSED RAT HEARTS", Br. J. Pharmacol., 1988, 93, 247P, where utility in protecting hearts from the potentially lethal biochemical and functional injury produced by ischaemia and/or reperfusion was reported. Tissue protection, however, is not achieved by a calcium entry blockade nor by a beta-blockade mechanism (Brown et al., Br. J. Pharmacol., 1988, 93, 248P), nor would such active agents be expected to have a tissue protective effect. Moreover, cardiodepression has been identified as a limiting factor for extensive use of CEBs in the treatment of cardio-related ischaemic conditions (Packer, et al., Circn., 75(V), 56-64, 1987; Barjon, et al., J. Am. Coll. Cardiol., 9, 622-630, 1987).

One aspect of the present invention concerns a use involving the treatment of tissues experiencing a physical or chemical insult, by administering an effective amount of a compound of Formula I:



(Formula I)

and the pharmaceutically acceptable esters and acid addition salts thereof, wherein:

R^1, R^2, R^3, R^4 and R^5 are each independently hydrogen, lower alkyl, lower alkoxy, cyano, trifluoromethyl, halo, lower alkylthio, lower alkyl sulfinyl, lower alkyl sulfonyl, N-optionally substituted alkylamido, except that when R^1 is methyl, R^4 is not methyl; or

R^2 and R^3 together form $-OCH_2O-$;

R^6, R^7, R^8, R^9 and R^{10} are each independently hydrogen, lower acyl, aminocarbonylmethyl, cyano, lower alkyl, lower alkoxy, trifluoromethyl, halo, lower alkylthio, lower alkyl sulfinyl, lower alkyl sulfonyl, di-lower alkyl amino;

R^6 and R^7 together form -CH=CH-CH=CH-; or

R^7 and R^8 together form $-OCH_2O-$;

R^{11} and R^{12} are each independently hydrogen or lower alkyl; and

W is oxygen or sulfur.

In a preferred embodiment, the invention entails a use wherein the compound of Formula I is one in which R^1 and R^5 are methyl, particularly where R^2, R^3, R^4, R^{11} and R^{12} are hydrogen, and more particularly where W is oxygen. Most preferred is the use of ranolazine, i.e., where R^6 is methoxy and R^7, R^8, R^9 and R^{10} are hydrogen.

The present invention presents a method for preserving donor tissues used in transplants (protecting them from the deleterious effects of ischaemia), by administration to the donor, the recipient and/or by adding to the ex-vivo perfusion fluid an effective amount of a compound of Formula I, preferably ranolazine or a pharmaceutically acceptable salt thereof, particularly for renal transplants, skin grafts, cardiac transplants, lung transplants, corneal transplants, and liver transplants.

In yet another aspect, the invention relates to pharmaceutical compositions containing a therapeutically effective amount (up to 5 mg/ml for liquid and semi-solid formulations) of a compound of Formula I, particularly ranolazine or a pharmaceutically acceptable salt thereof. admixed with at least one pharmaceutically acceptable excipient, such compositions being adapted for use in the methods of treatment of the present invention.

Another aspect of the invention entails methods of treatment by coadministration of a compound of Formula I together with another pharmaceutically active agent, such as thrombolytic agents [especially TPA (Tissue Plasminogen Activator) or streptokinase] or anti-anginals (such as beta blockers, including propranolol and timolol).

Definitions and General Parameters

The following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

As used herein, the term "treatment" or "treating" means any treatment of a disease in a mammal, including:

(i) preventing the disease, that is, causing the clinical symptoms of the disease not to develop;
(ii) inhibiting the disease, that is, arresting the development of clinical symptoms; and/or
(iii) relieving the disease, that is, causing the regression of clinical symptoms.

As used herein, the term "q.s." means adding a quantity sufficient to achieve a stated function, e.g., to bring a solution to the desired volume (i.e., 100%).

As used herein, the term "effective amount" means a dosage sufficient to provide treatment for the disease state being treated. This will vary depending on the patient, the disease and the treatment being effected.

Preparation of Ranolazine

Ranolazine and the piperazine compounds of Formula I can be prepared, for example, as described in U.S. Patent No. 4,567,264.

Utility, Testing and Administration

It has surprisingly been found that ranolazine is active in methods of treatment unrelated to its initially identified calcium entry blocking mechanism and cardioselective indications. Particularly interesting is the fact that ranolazine has now been found to protect tissues against ischaemia (improving cellular oxygen utilization efficiency) at doses that do not produce any cardiodepressant effects (see, Allely and Alps, supra, and Ferrandon, et al., supra.)

General Utility

The piperazine compounds of Formula I, particularly ranolazine and the pharmaceutically acceptable salts thereof (preferably the dihydrochloride), are useful for treating tissues experiencing a physical or chemical insult. For example, such treatment can be for cardioplegia, or for hypoxic reperfusion injury to cardiac or skeletal muscles, or brain tissue. The compounds of Formula I, particularly ranolazine and its salts, are also useful for preserving (e.g., preventing deterioration of) donor tissues used in transplants, by administration to the transplant donor, to the transplant recipient, or by perfusion of the tissues to be transplanted, particularly for renal transplants, skin grafts, cardiac transplants, lung transplants, corneal transplants, and liver transplants.

Testing

Protection of the myocardium against ischaemic damage is experimentally demonstrated by inducing infarction in a suitable test animal (e.g., a baboon) followed by examination of insult-induced elevations in enzyme levels (particularly creatine kinase "CK" (also known as creatine phosphokinase, "CPK") and lactate dehydrogenase "LDH"). It is accepted that concentrations of these enzymes are increased after myocardial damage (Galen, et al., J.A.M.A., 232, 145-147, 1975) and that such enzyme levels can be obtained by an experimental model under conditions which are adapted from the one described by Alps, et al., (Arzneim. Forsch Drug Res., 33, (1), 6, 868-876, 1983). The actual measurement of enzyme levels is made by the method of Galen (Med. Times, 105(2), 89-99, 1977). The compounds of Formula I, as exemplified by ranolazine, are active in reducing CK and LDH enzyme levels as measured by this assay.

Protection against myocardial ischaemia can also be assessed via effectiveness to prevent ischaemia-induced increase in alpha-1 adrenoceptor number in the myocardium. It is known that alpha-1 adrenoceptor population increases in the myocardium suffering from ischaemia (Heathers, et al., Circulation Research, 61, 735-746, 1987). It

has also been shown that alpha-1 adrenoceptor antagonists have beneficial effects during ischaemia in animal models (Wilbur, et al., J. Cardiovascular Pharmacol., 10, 96-106, 1987). Thus agents which prevent the ischaemia-induced increase in alpha-1 adrenoceptors density are beneficial during myocardial ischaemia. The ability of compounds of Formula 1, as exemplified by ranolazine, to inhibit the ischaemia-induced increase of alpha-1 adrenoceptors in myocardium is assessed in the rat left ventricle using a model of ischaemia described by Allely and Brown (Br. J. Pharmacol., 95, 705P, 1988) and the method of Williams et al. (Cardiovascular Pharmacology, 3, 522, 1981) for measuring alpha-1-adrenoreceptor density. A detailed description is set forth in Example 6.

Protection of skeletal muscles against damage resulting, for example, from major surgical practices. was experimentally assessed in the same model used to assess its protective effects at the myocardial level. For this purpose skeletal muscle-specific isoenzymes CPK_3 and LDH_5, are assayed as indications of damaged muscle according to the method of Galen, (Med. Times, 105(2), 89-99, 1977). A detailed description is set forth in Example 2.

Protection of the myocardium against deleterious effects of ischaemia induced by open-heart and other cardiac surgical procedures, including cardioplegia, is assessed by a method modified from Langendorff, which entails measuring coronary effluent pH and lactate level. These tracers are recognised as indicative of tissue damage induced by severe reduction in the nutrient supply to the heart (Armiger, et al., Biochem. Med., 29, 265-267, 1983; van Gilst, et al., Archives of Pharmacol., suppl., 330, 161P, 1985). A detailed description is set forth in Example 3.

The utility of compounds of Formula I, as exemplified by ranolazine, in organ transplant is demonstrated by administering the test compound to pigs before nephrectomy, and/or by adding the compound to the fluid used for flushing and storage of the organ and by assessing functionality of transplanted kidneys over a period of 14 days. Improvement of renal function in treated animals is assessed by measurement of the glomerular filtration rate and also by peak serum levels for creatinine and urea. Glomerular filtration is a well established indicator of renal function (see, e.g., Mudge and Weiner in The Pharmacological Basis of Therapeutics, Goodman and Gilman, 879, 7th Ed, 1985) and it is generally assessed by measurement of inulin and/or creatinine clearance (Textbook of Medicine, 1088-93, 14th Ed., 1975 - Beeson and McDermott Editors). A detailed description is set forth in Example 4.

Cerebral ischaemia is the result of either a generalized or a localized prolonged reduction of blood flow to the brain. Such a blood flow reduction can result from various pathological conditions including cerebral venous inflammation and thrombosis, cardiac diseases, changes in blood (clotting, viscosity, anaemia) or from cardiac surgical practices. One of the indications of damage produced by cerebral ischaemia is the increase of the iso-enzyme creatinephosphokinase 1 (CPK_1) in the plasma (Rossi, et al., Am. J. Cardiol., 58(13), 1236-1241, 1986). Inhibition of the peripheral appearance of CPK_1 is an indication of reduced damage caused by ischaemia to the brain. This is demonstrated by administration of a test compound prior to coronary artery ligation in the baboon, as a bolus i.v. injection followed by an infusion over the period of reperfusion, as described by Alps, et al., (Arzneim. Forsch Drug Res., 33, (1), 6, 868-876, 1983).

Administration

Administration of ranolazine in pure form or in an appropriate pharmaceutical composition can be carried out via any of the accepted modes of administration of agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally or topically, including by perfusion. Administration can be achieved in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, capsules, powders, solutions, suspensions, emulsions, creams, lotions, aerosols, ointments or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The compositions will include a conventional pharmaceutical carrier or excipient and an effective amount of ranolazine or a pharmaceutically acceptable salt thereof, and in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc. Sustained release and slow release formulations for maintaining extended or constant dosage levels are also useful in the present invention. Ranolazine can also be co-administered with other active agents, such as thrombolytic agents [especially TPA (Tissue Plasminogen Activator) or streptokinase] or anti-anginals (such as beta blockers, including propranolol and timolol).

The preferred method of administration is parenteral, except for those cases when the subject must be pre-treated before surgery or when the subject must be maintained under therapy after acute episodes of ischaemia (in which instances it may be preferable to administer the composition orally).

Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of the pharmaceutically active compound of this invention and 99% to 1% by weight of suitable pharmaceutical excipients. Preferably, the composition will be about 5 to 75% by weight of a pharmaceutically active compound, with the rest being suitable pharmaceutical excipients. For liquid and semi-solid formulations, about 5 mg/ml is preferred as the maximum concentration for the active ingredient.

Oral administration entails using a convenient daily dosage regimen which can be adjusted according to the degree of affliction. For such oral administration, a pharmaceutically acceptable, non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, gelatin, sucrose, magnesium carbonate,

and the like. Such compositions take the form of solutions, suspensions. tablets, capsules, powders, sustained release or slow release formulations and the like.

Preferably the oral compositions will take the form of a capsule or tablet and thus the composition will contain, along with the active ingredient, a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant such as starch or derivatives thereof; a lubricant such as magnesium stearate and the like; and a binder such as a starch, gum acacia, polyvinylpyrrolidone, gelatin, cellulose and derivatives thereof, and the like.

The active compounds may be formulated into a suppository using, for example, about 0.5% to about 50% active ingredient disposed in a carrier of polyethylene glycols (PEG) [e.g., PEG 1000 (96%) and PEG 4000 (4%)] or semi-synthetic glycerides (Witepsol™, Suppocire™).

Another preferred mode of administration is parenterally. Liquid pharmaceutically administerable compositions can, for example, be prepared by dissolving, dispersing, etc. an active compound (about 0.5% to about 20%), as described above, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension.

For preservation of tissues awaiting transplantation, a perfusion solution is preferred. Such solutions include an active compound in a carrier such as Eurocollins Solution (Fresenius, A.G., Bad Homburg, vdH, Germany), University of Wisconsin Fluid (Kalayoglu, M., et al., The Lancet, 1988 i, 617), phosphate buffered sucrose (see, e.g., Example 7E) and Hyperosmolar Citrate (Ross, et al., Transplantation, 1976, 498-501).

If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc.

Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 16th Ed., (Mack Publishing Company, Easton, Pennsylvania, 1980). The composition to be administered will, in any event, contain a quantity of the active compound(s) in a pharmaceutically effective amount for relief of the particular condition being treated when administered in accordance with the teachings of this invention.

Example 2 describes oral and parenteral formulations containing ranolazine. Such formulations should not be construed as narrowing the invention. In particular, parenteral formulations can be given as dilutions with perfusion fluids, dialysis fluids and/or fluids used to blush and store organs. It is also intended that the invention encompasses the possibility to associate ranolazine with other pharmaceutical agents, as co-prescription or by concomitant dissolution in fluids.

Dosage

Generally, ranolazine is administered in a therapeutically effective amount, i.e., a dosage sufficient to effect treatment. The amount of active compound administered will, of course, be dependent on the subject treated, the subject's weight, the severity of the affliction, the route of administration and the judgement of the prescribing physician. However, absent sufficient time to weigh the foregoing factors in detail, e.g., in emergency situations, effective i.v. dosages range from about 0.05 to about 5 mg/kg for bolus injection followed by an infusion ranging from about 0.3 to about 30 mg/kg/hour. Preferably, the i.v. bolus dosage ranges from about 0.1 to about 2.5 mg/kg and the infusion dosage from about 1.5 to about 15 mg/kg/hour. For an average 70 kg human, the i.v. bolus would range from about 3.5 to about 350 mg, or preferably from about 15 to about 105 mg. In other situations, the oral dosage is in the range of about 35 to about 1400 mg per day, preferably about 70 to about 700 mg/day, for an average 70 kg human. For administration by perfusion fluid, a concentration of about 0.001 to about 5 g per litre is used, preferably about 0.005 to about 2.5 g per litre, and most preferably about 0.005 to about 0.1 g per litre; perfusion can continue from tissue removal from the donor until its use for transplantation.

EXAMPLES

The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

EXAMPLE 1

Protection For Organ Transplants

Twenty left nephrectomised pigs were autotransplanted with their kidneys after preservation for 24 hours in phosphate buffered sucrose (PBS 140) and immediate contralateral nephrectomy followed the autotransplantation.

The quality of the preservation and post-transplant renal function were assessed by measurement of glomerular filtration rate (GFR) using inulin clearance on day 7.

Group A (n=10) placebo group

The animals received placebo pre-treatment (bolus and infusion) commencing 5 min prior to left nephrectomy and lasting until the kidney was removed. The kidney was then flushed with PBS 140 containing placebo before storage in PBS 140. After 24 hours storage the kidney was auto-transplanted.

Group B (n=10) treated group

The animals received a bolus dose of ranolazine intravenously (0.85mg/kg) 5 min prior to nephrectomy followed by an infusion (0.25mg/kg/h) until the kidney was removed. The kidney was then flushed with PBS 140 solution containing ranolazine 0.5mg/l (made up immediately before flush) prior to storage. After 24 hours storage the kidney was auto-transplanted.

Table 5

	Group A	Group B
Glomerular filtration rate at day 7	16.4ml/min	56.6ml/min
Peak Serum Urea	43.4mM/l	28.5mM/l
Peak Serum Creatinine	1063µM/l	750µM/l

The results shown in Table 5 demonstrate that organs preserved in a fluid containing ranolazine achieved superior functionality after transplantation as compared with the control group that did not receive ranolazine.

EXAMPLE 2

Formulations

The following example illustrates the preparation of representative pharmaceutical formulations containing a compound of Formula I, as exemplified by ranolazine.

A. I.V. FORMULATION (low concentration)		
(ranolazine)	5.0 mg	0.5 g
dextrose monohydrate	51.2 mg	5.1 g
sodium hydroxide q.s. to	pH 4	pH 4
water for injection to	1.0 ml	100 ml

B. I.V. FORMULATION (high concentration)		
(ranolazine)	20.0 mg	2 g
dextrose monohydrate	39.4 mg	4 g
sodium hydroxide q.s. to	pH 4	pH 4
water for injection to	1.0 ml	100 ml

To prepare the I.V. formulations, ranolazine and dextrose monohydrate are dissolved into water (70 per cent of the final desired volume) then sodium hydroxide (10N solution) is added under stirring until pH 4 and the volume is completed to 100 ml with water. The medium is filtered through a 0.2 micron membrane filter and packaged in ampoules or vials under sterile conditions. Alternatively the medium can be filtered under non-sterile conditions, packed in ampoules then sterilized by autoclaving.

C. FILM COATED TABLET FORMULATION	
Ingredients	Parts by weight
ranolazine HCl (A)	80.0
microcrystalline cellulose (B)	16.5
polyvinylpyrrolidone (C)	1.0
crosscarmellose sodium (D)	2.0
magnesium stearate (E)	0.5

(A), (B) and half of (D) are mixed then (C) and water are added to allow wet granulation. (E) and the remaining part of (D) are finally added. After careful mix the granulated mixture is dried, formed into tablets containing up to 250 mg of active compound, and the tablets are film coated using White Opadry™ following appropriate techniques.

D. CONTROLLED RELEASE FORMULATION	
Ingredients	Parts by weight
ranolazine BASE (A)	90
microcrystalline cellulose (B)	10

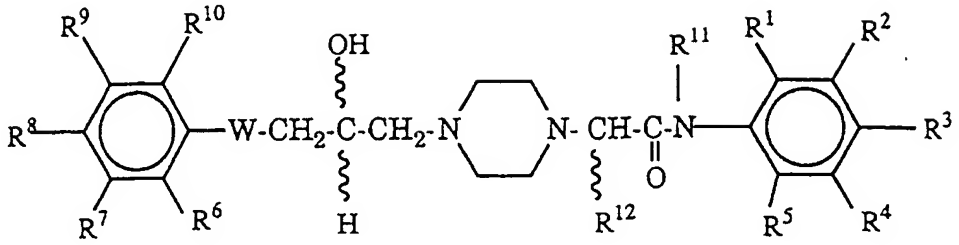
The two above ingredients are dry mixed then water is added to form a wet mass adequate for extrusion then spheronisation (0.5 to 1.4 mm). Microspheres are coated with appropriate release-controlling polymers then put into hard shell capsules containing up to 250 mg of active ingredient per unit.

E. PERFUSION FLUID	
Ingredients	Parts by weight
Ranolazine	20 mg
Phosphate Buffered Sucrose:	
Sucrose	48.0 g
Sodium Dihydrogen Phosphate	4.59 g
Sodium Monohydrogen Phosphate	6.53 g
Water For Injection (U.S.P.)	q.s. to 1000 ml

The ingredients are dissolved in a portion of the Water For Injection, and once dissolved, the remaining volume is made up with Water For Injection.

Claims

1. The use of a compound of the formula:



or pharmaceutically acceptable esters or acid addition salts thereof, wherein:

R^1, R^2, R^3, R^4 and R^5 are each independently hydrogen, lower alkyl, lower alkoxy, cyano, trifluoromethyl, halo, lower alkylthio, lower alkyl sulfinyl, lower alkyl sulfonyl, N-optionally substituted alkylamido, except that when R^1 is methyl, R^4 is not methyl; or
R^2 and R^3 together form $-OCH_2O-$;
R^6, R^7, R^8, R^9 and R^{10} are each independently hydrogen, lower acyl, aminocarbonylmethyl, cyano, lower alkyl, lower alkoxy, trifluoromethyl, halo, lower alkylthio, lower alkyl sulfinyl, lower alkyl sulfonyl, di-lower alkyl amino;
R^6 and R^7 together form $-CH=CH-CH=CH-$; or
R^7 and R^8 together form $-OCH_2O-$;
R^{11} and R^{12} are each independently hydrogen or lower alkyl; and
W is oxygen or sulfur;

in the manufacture of a medicament for preserving donor tissues in transplants.

2. Method of preserving a donor tissue in transplants by adding an effective amount of a compound as defined in claim 1 to the ex-vivo perfusion fluid.

3. The use or method of Claim 1 or 2 wherein R^1 and R^5 are methyl.

4. The use or method of Claim 3 wherein R^2, R^3, R^4, R^{11} and R^{12} are hydrogen.

5. The use or method of Claim 4 wherein W is oxygen.

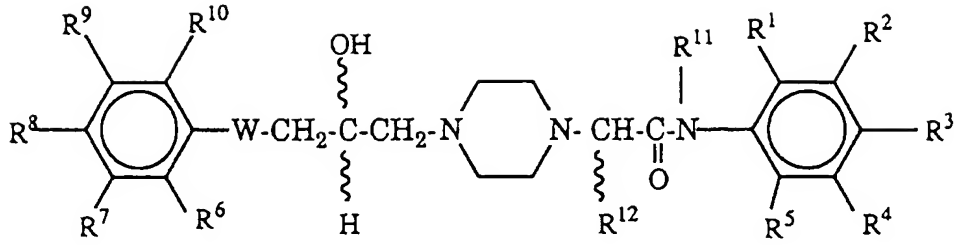
6. The use or method of Claim 5 wherein R^6 is methoxy and R^7, R^8 R^9 and R^{10} are hydrogen, i.e., ranolazine.

7. The use or method of any one of Claims 1-6 wherein a medicament for preserving donor tissues used in transplant, preferably renal transplants, skin grafts, cardiac transplants, lung transplants, corneal transplants, or liver transplants, is prepared.

8. The use or method of any one of Claims 1-7 wherein said compound is ranolazine, or a pharmaceutically acceptable salt thereof.

9. The or method use of any one of Claims 1-8 which comprises the combined use of said compound together with a second pharmaceutically active agent, such as TPA or streptokinase.

10. A pharmaceutical composition comprising a perfusion fluid containing a therapeutically affective amount, up to 5 mg/ml for liquid and semi-solid formulations, of a compound of the formula:



or pharmaceutically acceptable esters or acid addition salts thereof, wherein:

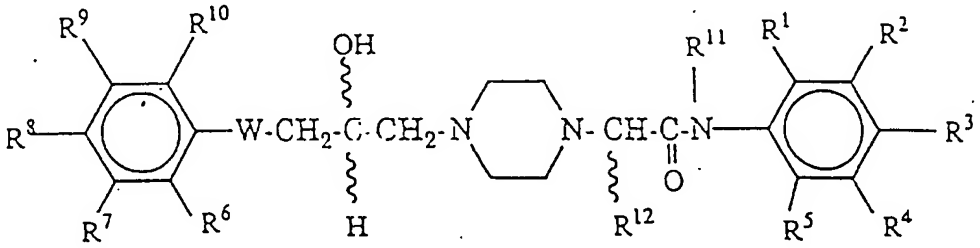
R^1, R^2, R^3, R^4 and R^5 are each independently hydrogen, lower alkyl, lower alkoxy, cyano, trifluoromethyl, halo, lower alkylthio, lower alkyl sulfinyl, lower alkyl sulfonyl, N-optionally substituted alkylamido, except that when R^1 is methyl, R^4 is not methyl; or
R^2 and R^3 together form $-OCH_2O-$;
R^6, R^7, R^8, R^9 and R^{10} are each independently hydrogen, lower acyl, aminocarbonylmethyl, cyano, lower alkyl, lower alkoxy, trifluoromethyl, halo, lower alkylthio, lower alkyl sulfinyl, lower alkyl sulfonyl, di-lower alkyl amino;
R^6 and R^7 together form $-CH=CH-CH=CH-$; or
R^7 and R^8 together form $-OCH_2O-$;
R^{11} and R^{12} are each independently hydrogen or lower alkyl; and
W is oxygen or sulfur,

admixed with at least one pharmaceutically acceptable excipient.

11. The pharmaceutical composition of Claim 9 wherein said compound is ranolazine.

Patentansprüche

1. Verwendung einer Verbindung der Formel:



oder pharmazeutisch annehmbarer Ester oder Säureadditions-Salze davon, worin:

R^1, R^2, R^3, R^4 und R^5 jeweils unabhängig für Wasserstoff, Niederalkyl, Niederalkoxy, Cyano, Trifluormethyl, Halogen, Niederalkylthio, Niederalkylsulfinyl, Niederalkylsulfonyl, N-gegebenenfalls substituiertes Alkylamido stehen, mit der Ausnahme, daß wenn R^1 Methyl ist, R^4 nicht Methyl ist; oder
R^2 und R^3 zusammen $-OCH_2O-$ bilden;
R^6, R^7, R^8, R^9 und R^{10} jeweils unabhängig für Wasserstoff, Niederacyl, Aminocarbonylmethyl, Cyano, Niederalkyl, Niederalkoxy, Trifluormethyl, Halogen, Niederalkylthio, Niederalkylsulfinyl, Niederalkylsulfonyl, Dinieder-alkylamino stehen;
R^6 und R^7 zusammen $-CH=CH-CH=CH-$ bilden; oder
R^7 und R^8 zusammen $-OCH_2O-$ bilden;
R^{11} und R^{12} jeweils unabhängig für Wasserstoff oder Niederalkyl stehen; und
W Sauerstoff oder Schwefel ist;

bei der Herstellung eines Medikaments für die Konservierung von Spender-Geweben in Transplantaten.

2. Verfahren zur Konservierung eines Spender-Gewebes in Transplantaten durch Zugabe einer effektiven Menge einer Verbindung wie in Anspruch 1 definiert zu dem ex vivo-Perfusionsfluid.

3. Verwendung oder Verfahren nach Anspruch 1 oder 2, worin R^1 und R^5 Methyl bedeuten.

4. Verwendung oder Verfahren nach Anspruch 3, worin R^2, R^3, R^4, R^{11} und R^{12} für Wasserstoff stehen.

5. Verwendung oder Verfahren nach Anspruch 4, worin W für Sauerstoff steht.

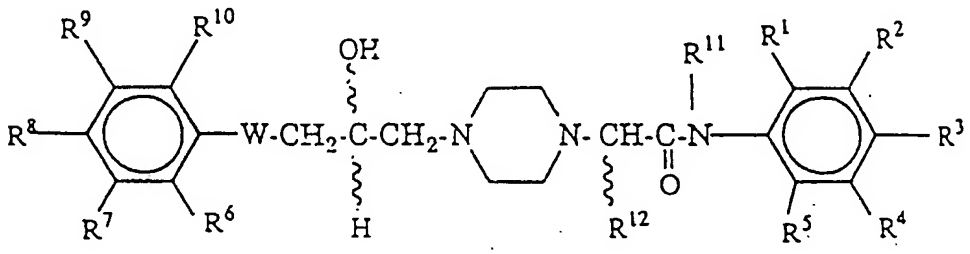
6. Verwendung oder Verfahren nach Anspruch 5, worin R^6 Methoxy ist und R^7, R^8, R^9 und R^{10} Wasserstoff darstellen, d.h. Ranolazin.

7. Verwendung oder Verfahren nach irgendeinem der Ansprüche 1 - 6, worin ein Medikament zur Konservierung von in einem Transplantat verwendeten Spender-Geweben, vorzugsweise Nieren-Transplantaten, Haut-Transplantaten, Herz-Transplantaten, Lungen-Transplantaten, Hornhaut-Transplantaten oder Leber-Transplantaten, hergestellt wird.

8. Verwendung und Verfahren nach irgendeinem der Ansprüche 1 - 7, worin die Verbindung Ranolazin oder ein pharmazeutisch annehmbares Salz davon ist.

9. Verwendung oder Verfahren nach irgendeinem der Ansprüche 1 - 8, welche bzw. welches die kombinierte Verwendung der Verbindung zusammen mit einem zweiten pharmazeutisch aktiven Mittel, wie beispielsweise TPA oder Streptokinase, umfaßt.

10. Pharmazeutische Zusammensetzung, umfassend ein Perfusionsfluid, das eine therapeutisch effektive Menge, bis zu 5 mg/ml für flüssige und halbfeste Formulierungen, einer Verbindung der Formel:



oder von pharmazeutisch annehmbaren Estern oder Säureadditions-Salzen davon,
worin:

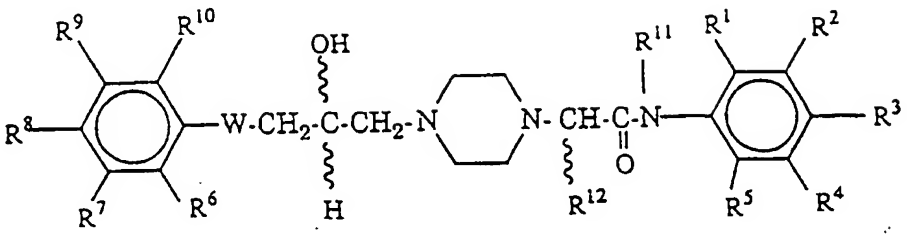
R^1, R^2, R^3, R^4 und R^5 jeweils unabhängig für Wasserstoff, Niederalkyl, Niederalkoxy, Cyano, Trifluormethyl, Halogen, Niederalkylthio, Niederalkylsulfinyl, Niederalkylsulfonyl, N-gegebenenfalls substituiertes Alkylamido stehen, mit der Ausnahme, daß wenn R^1 Methyl ist, R^4 nicht Methyl ist; oder
R^2 und R^3 zusammen $-OCH_2O-$ bilden;
R^6, R^7, R^8, R^9 und R^{10} jeweils unabhängig für Wasserstoff, Niederacyl, Aminocarbonylmethyl, Cyano, Niederalkyl, Niederalkoxy, Trifluormethyl, Halogen, Niederalkylthio, Niederalkylsulfinyl, Niederalkylsulfonyl, Dinieder-alkylamino stehen;
R^6 und R^7 zusammen $-CH=CH-CH=CH-$ bilden; oder
R^7 und R^8 zusammen $-OCH_2O-$ bilden;
R^{11} und R^{12} jeweils unabhängig für Wasserstoff oder Niederalkyl stehen; und
W für Sauerstoff oder Schwefel steht;

in Mischung mit wenigstens einem pharmazeutisch annehmbaren Exzipienten enthält.

11. Pharmazeutische Zusammensetzung nach Anspruch 9, in welcher die Verbindung Ranolazin ist.

Revendications

1. Utilisation d'un composé de formule :



ou de ses esters ou sels d'addition d'acides pharmaceutiquement acceptables, formule dans laquelle :

R^1, R^2, R^3, R^4 et R^5 représentent chacun indépendamment l'hydrogène, un groupe alkyle inférieur, alkoxy inférieur, cyano, trifluorométhyle, halogéno, alkylthio inférieur, alkysulfinyle inférieur, alkylsulfonyle inférieur, alkylamido facultativement N-substitué, sous réserve que, lorsque R^1 représente un groupe méthyle, R^4 ne représente pas un groupe méthyle ; ou
R^2 et R^3 forment conjointement un groupe $-OCH_2O-$;
R^6, R^7, R^8, R^9 et R^{10} représentent chacun indépendamment l'hydrogène, un groupe acyle inférieur, aminocarbonylméthyle, cyano, alkyle inférieur, alkoxy inférieur, trifluorométhyle, halogéno, alkylthio inférieur, alkylsulfinyle inférieur, alkylsulfonyle inférieur, di-(alkyle inférieur)-amino ;
R^6 et R^7 forment conjointement un groupe -CH=CH-CH=CH-; ou
R^7 et R^8 forment conjointement un groupe $-OCH_2O$;
R^{11} et R^{12} représentent chacun indépendamment l'hydrogène ou un groupe alkyle inférieur ; et
W représente l'oxygène ou le soufre ;

dans la production d'un médicament destiné à préserver des tissus de donneurs dans des transplants.

2. Procédé pour préserver un tissu de donneur dans des transplants par addition d'une quantité efficace d'un composé répondant à la définition suivant la revendication 1 au fluide de perfusion ex-vivo.

3. Utilisation ou procédé suivant la revendication 1 ou 2, dans lequel R^1 et R^5 représentent des groupes méthyle.

4. Utilisation ou procédé suivant la revendication 3, dans lequel R^2, R^3, R^4, R^{11} et R^{12} représentent l'hydrogène.

5. Utilisation ou procédé suivant la revendication 4, dans lequel W représente l'oxygène.

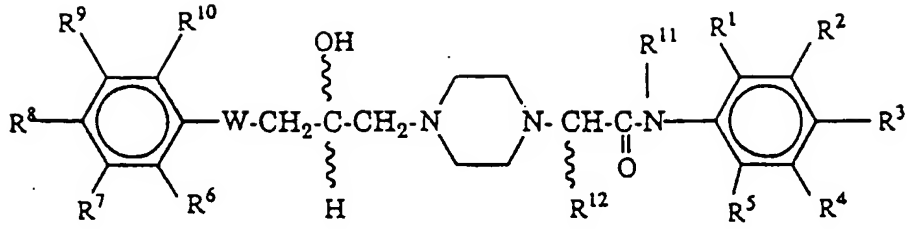
6. Utilisation ou procédé suivant la revendication 5, dans lequel R^6 représente un groupe méthoxy et R^7, R^8, R^9 et R^{10} représentent l'hydrogène, ce qui signifie que le composé consiste en ranolazine.

7. Utilisation ou procédé suivant l'une quelconque des revendications 1 à 6, dans lequel un médicament destiné à préserver des tissus de donneurs utilisés dans des transplants, de préférence des transplants rénaux, des greffes cutanées, des transplants cardiaques, des transplants pulmonaires, des transplants cornéens ou des transplants hépatiques, est préparé.

8. Utilisation ou procédé suivant l'une quelconque des revendications 1 à 7, dans lequel le composé consiste en ranolazine ou un de ses sels pharmaceutiquement acceptables.

9. Utilisation ou procédé suivant l'une quelconque des revendications 1 à 8, qui comprend l'utilisation mixte du composé conjointement avec un second agent pharmaceutiquement actif, tel que l'activateur tissulaire du plasminogène (TPA) ou la streptokinase.

10. Composition pharmaceutique comprenant un fluide de perfusion contenant une quantité thérapeutiquement efficace, allant jusqu'à 5 mg/ml pour des formulations liquides et des formulations semi-solides, d'un composé de formule :



ou d'un de ses esters ou sels d'addition d'acides pharmaceutiquement acceptables, formule dans laquelle :

R^1, R^2, R^3, R^4 et R^5 représentent chacun indépendamment l'hydrogène, un groupe alkyle inférieur, alkoxy inférieur, cyano, trifluorométhyle, halogéno, alkylthio inférieur, alkysulfinyle inférieur, alkylsulfonyle inférieur, alkylamido facultativement N-substitué, sous réserve que, lorsque R^1 représente un groupe méthyle, R^4 ne représente pas un groupe méthyle ; ou
R^2 et R^3 forment conjointement un groupe $-OCH_2O$;
R^6, R^7, R^8, R^9 et R^{10} représentent chacun indépendamment l'hydrogène, un groupe acyle inférieur, aminocarbonylméthyle, cyano, alkyle inférieur, alkoxy inférieur, trifluorométhyle, halogéno, alkylthio inférieur, alkylsulfinyle inférieur, alkylsulfonyle inférieur, di-(alkyle inférieur)-amino ;
R^6 et R^7 forment conjointement un groupe -CH=CH-CH=CH-; ou
R^7 et R^8 forment conjointement un groupe $-OCH_2O-$;
R^{11} et R^{12} représentent chacun indépendamment l'hydrogène ou un groupe alkyle inférieur ; et
W représente l'oxygène ou le soufre ;

en mélange avec au moins un excipient pharmaceutiquement acceptable.

11. Composition pharmaceutique suivant la revendication 9, dans laquelle le composé consiste en ranolazine.